THIS IS AN ABSTRACT FOR "JP45014056"

This corresponds to Japanese granted patent # JP70/014056 (Imperial Yr.); the US equivalent is 3,683,091.

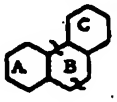
32,083 10.11.66 SHIO

PHENANTHRENE COMPOUNDS; ANTI-ANDROGENS

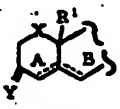
NE.67,15331 clg. 10.11.66(5); 2.12.66; 20.12.66; 28.12.66; 16.3.67; 14.6.67 (JA) as 73928/66 etc. Pub. 13.5.68 Shionogi & Co. Ltd.

NEW

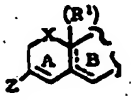
Phenanthrene compounds of general formula (I), of which the left hand side corresponds to parts 2-4 and the right hand side to parts 5-7, and their salts and quaternary compounds.



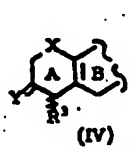
(I)



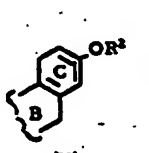
(II)



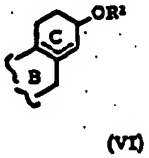
(III)



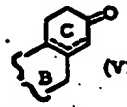
(IV)



(V)



(VI)



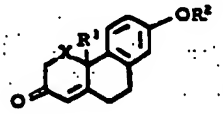
(VII)

R^1=H-, C_{1-4} alkyl, alkenyl- or alkynyl-
R^2=H-, methyl-
R^3=H-, C_{1-4} alkyl-, alkenyl- or alkynyl-
X=presence or absence of $-CH_2-$
Y= 

32,083 contd..

R^4=H-, acyl-
or O, N-group next to ketone e.g oxime ketal or 
R^5= C_{1-4} alkyl-, alkenyl-, alkynyl-
Z=tert.amino-, acyloxy-, C_{1-4} alkyloxy-
dotted line = presence or absence of a double bond
(R^1)=absence of R^1 if there is a double bond at 4a

for instance compound



(VIII)

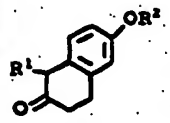
USES

Anti-androgen, anti-myogen, anti-thymolytic without other hormone activity. For treatment of hirsutism.

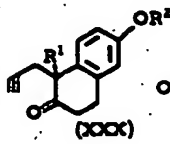
PREPARATION

To prepare compound (VIII)

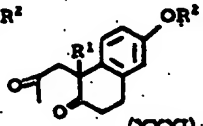
a) Compound of formula (XXX) is reacted in the presence of a basic catalyst with a propargyl halide $CH{\equiv}C.CH_2.X'$ (where X'=hal) to yield the 1-propargyl-tetralon derivative (XXX) which on hydration with say H_2SO_4 forms the 1-acetonyltetralone derivative (XXXI). By intramolecular condensation the latter is converted to a benzindene derivative (XXXII)



(XXX)



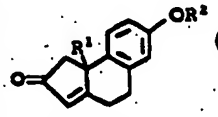
(XXX)



(XXXI)

32,083 contd..

32,083 cont'd..

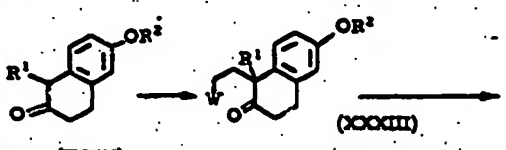


(XXXII)

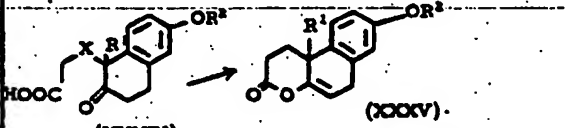
b) Hydrolysis of corresponding cpd. in which R^2=CH_3-

To prepare an optically active compound (VIII)

Compound of formula (XXX) is reacted with acrylonitrile or methyl- or ethylacrylate in the presence of a basic catalyst to yield cpd. (XXXIII) which is hydrolysed to cpd. (XXXIV). The latter is reacted with an optically active amine e.g cinchonidine and the corresponding amine salt is resolved into its isomers by fractional crystallisation. The two optically active salts are converted to the free acids, each of these being subjected to enollacton formation to yield the optically active compound (XXXV). This is subjected to a Grignard reaction with a methylmagnesiumhalogenide and finally the intermediate cpd. (XXXVI) formed is dehydrated to close the ring, using an acid or a base.



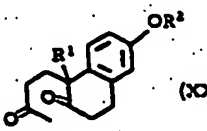
(XXX) (XXXIII)



(XXXIV) (XXXV).

32,083 cont'd..

32,083 cont'd..



(XXXVI)

W= -CN, -$COOCH_3$ or -$COOC_2H_5$.

EXAMPLE

A mixture of 1,2,3,4-tetrahydro-1-ethyl-6-methoxy naphthalenon-2 and sodium hydride in dry benzene is refluxed in a nitrogen atmosphere for 30 minutes. A solution of propargylbromide in benzene is added dropwise during 40 minutes and stirring of the reaction mixture is continued at room temperature for 1 hour, then a further 2 hrs. under reflux boiling. After allowing to stand overnight, the mixture is poured into ice-water. The product is extracted with ether, washed with water, dried over Na_2SO_4 and distilled to dryness in vacuo to yield an oily residue. This is chromatographed through aluminium oxide. Fractional distillation of the eluate with pentane-benzene yields 1,2,3,4-tetrahydro-1-ethyl-1-propargyl-6-methoxy naphthalenon-2(30).

A mixture of this product with water and Hg-Dowex-50 in dry methanol is vigorously stirred for 2 hours under a nitrogen atmosphere at 40-50°C. The reaction mixture is poured into ice water. The product is extracted with ether, washed with water, dried over Na_2SO_4 and distilled to yield an oily residue. This is dissolved in acetone and Hg-Dowex-50 added to it. The mixture is stirred in a nitrogen atmosphere for 10 minutes at 40-50°C. The reaction mixture is worked up as before and precipitation by fractional distillation in vacuo yields 1,2,3,4-tetrahydro-1-ethyl-1-acetonyl-6-methoxy-naphthalenon-2(31).

A solution of this product in dry methanol is a added in a nitrogen atmosphere to a stirred soln. of sodium methoxide in dry methanol. After stirring for 1½ hrs. at room temperature the

32,083 contd..

32,083 cont'd..

reaction mixture is refluxed for 1½ hrs. After cooling it is poured into ice water. The product is extracted with ether, washed with water dried over Na_2SO_4 and distilled to dryness yielding an oily residue. This is chromatographed over aluminium oxide and eluted with pentane-benzene. Recrystallisation from acetone-ether yields 2,4,5,9b-tetrahydro-7-methoxy-9b-ethyl-1H-benz(e) indenon-2 (32).